Remarks

After amendment, claims 6-9 and 25-30 are pending in the present application, claims 10-24 having been cancelled previously *without prejudice* pursuant to the Examiner's restriction requirement and Applicant's decision to elect with traverse to prosecute the invention of original claims 1-9. Claims 1-5 have been cancelled *without prejudice* in order to seek expedited allowance of the instant application. Upon the indication of allowable subject matter, and before the issuance of any patent from this application, Applicant will give consideration to filing a divisional application for the claimed subject matter previously cancelled.

The amendments to the claims have been made to indicate that the present methods are directed to the use of noribogaine as a non-addictive analgesic agent to treat pain with an opioid agonist (anti-nociceptive agent) without the addiction typical of opioid agonist analgesics such as morphine. Support for the amendments to the claims can be found throughout the originally filed application and claims and in particular, at page 3, second full paragraph, page 6, first paragraph and in particular, lines 4-5, and on page 9 in the examples section and in particular in the last paragraph at lines 20-23. No new matter has been added by way of the present amendment. Note that in addition to the specification clearly indicating that noribogaine is a full opioid agonist, the specification also clearly indicates that noribogaine is also an antinociceptive agent (i.e., an agent which eliminates or reduces nociceptive pain). See page 9, lines 20-23. Thus, the present application is directed to the unexpected discovery that noribogaine is a full opioid receptor agonist which acts as an antinociceptive agent, exhibiting antinociceptive activity similar to morphine's activity, without morphine's addiction to the patient. Thus, the present invention represents a clear advance in the art and is deserving of patent protection.

The Examiner has rejected the previously filed claims under 35 U.S.C.§112, first paragraph, §102(e) and 103 for the reasons which are stated in the September 26, 2005 final office action. For the reasons which are presented hereinbelow and the reasons presented in the attached declaration of inventor Dr. Deborah A. Mash, it is respectfully submitted that the amended claims address all of the Examiner's rejections and the claims are now in condition for allowance.

The courtesy of Examiner Jiang's interviewing the present application telephonically with the undersigned attorney in mid-October is respectfully acknowledged. Applicant respectfully submits that with the amendment to the claims of the present application, the application is now in condition for allowance and such action is earnestly solicited.

The §112, First Paragraph Rejection

The Examiner has rejected previously submitted claims 1-2, 4-9 and 25-30 under 35 U.S.C.§112, first paragraph for the reasons which are stated on page 3-4 of the September 26, office action. Note that Applicant has amended the term "pain treatable with an opioid agonist analgesic" to the term "pain with an opioid agonist" in order to address the Examiner's concerns about the original term. Although Applicant does not believe that the original term constituted new matter and that the specification clearly indicated that the type of pain being treated was nociceptive pain[1], Applicant has amended the claims to a term with which the Examiner is more comfortable in order to expedite allowance of this application. It is respectfully submitted with the amendment to claims 6 and 25 as presented, the claims are now in compliance with 35 U.S.C.§112, first paragraph and are fully supported by the originally filed specification and claims.

The §102(e) Rejection

The Examiner has rejected the previously filed claims under 35 U.S.C. §102(e) as being anticipated by Olney (U.S. patent no. 5,925,634). The Examiner recognizes that Olney discloses the use of ibogaine in the treatment of *neuropathic* pain. Given that Olney teaches the use of ibogaine to treat neuropathic pain and noribogaine is a metabolite of ibogaine, the Examiner concludes that the present claims are anticipated and therefore, unpatentable. Applicant respectfully traverses the Examiner's rejection.

As amended, the claims are directed to the use of noribogaine for the treatment of pain

1 As evidenced by the fact that the specification clearly indicates that noribogaine is replacing morphine in the treatment of pain, morphine treats nociceptive pain and is generally known as an anti-nociceptive agent and that noribogaine was shown to be an opoid agonist like morphine and can be used as an antinociceptive agent consistent with its anti-nociceptive activity- see, in particular, the example on page 9 and discussion at lines 20-23 of the present application.

as an opioid agonist, without addiction as set forth in the claims of the present application.. The present invention relates to the unexpected finding that noribogaine, acts to alleviate nociceptive pain in a patient by acting on the same receptors acted on by opioid agonists such as morphine, i.e., the μ receptor. Note that morphine and noribogaine are now both shown to be full μ receptor agonists which can be used as antinociceptive agents, but with noribogaine treating pain without morphine addiction. Thus, the present invention relates to the discovery that noribogaine is a non-addictive μ receptor agonist and can be used as a substitute for morphine without showing the same addictive side effects of morphine. Thus, the present invention represents a major advance in the art.

Olney, in complete contrast to the present invention, discloses the use of ibogaine as an NMDA antagonist for the treatment of *neuropathic* pain, which is pain which is mediated through NMDA receptors, not μ receptors as in the case of the present invention.

That Olney clearly does not anticipate the present invention is found in Olney's disclosure in the abstract on the first page of the patent as well as in column 7, lines 16-19. Those passages read:

> This invention discloses that ibogaine, a plant derivative, can be used safely to treat neuropathic pain (*i.e., pain which does not respond conventionally to opiate drugs such as morphine).* Emphasis ours.

Indeed, it was generally recognized in the art that neuropathic pain did not generally respond well to opioid agonist therapy. See, Hanks, *British Medical Bulletin,* 47, 3, 718-731 (1991); Kupers, et al., *Pain*, 47, 5-12 (1991); Cherny, et al., *Neurology,* 44, 857 (May, 1994); Martin and Hagan, *Journal of Pain Symptoms Management*, 14, 2, 99-117, (1997); Garcia and Altman, *Seminars in Arthritis and Rheumatism,* 27, 1, 1-16 (August, 1997); and Abstract, Shir, et al., *Harefuah,* 118, 8, 452-454 (1990), copies enclosed

Thus, Olney clearly does not teach the use of ibogaine as a substitute for an addictive opioid agonist such as morphine in the treatment of nociceptive pain because Olney recognized (as the art recognized- see the attached Declaration of inventor Dr. Deborah A. Mash), that ibogaine did not act at the receptors at which opioid agonists acted (i.e., μ receptors). Rather,

Olney teaches the use of ibogaine to treat neuropathic pain which is mediated through NMDA receptors by functioning as an antagonist of the NMDA receptor. Because the present claims are directed to the treatment of pain mediated through μ receptors as an opioid agonist, not as a NMDA receptor antagonist, no anticipation of the present invention by Olney is made out. Indeed, Olney clearly teaches away from the present invention.

As further evidence, Applicants point to the present specification and in particular, the example on pages 9 and 10, which evidences that noribogaine is a potent full μ receptor agonist similar in activity to morphine, whereas ibogaine evidenced extremely weak, virtually non-existent activity in the same assay, even at high concentrations above 100 μM. (more than 300 fold greater than the noribogaine used). Thus, ibogaine is not useful in the present invention and is not thought to be useful as an opioid agonist, whereas noribogaine unexpectedly has activity consistent with its use as a full opioid agonist and antinociceptive agent, *without* the addictive properties of morphine.

Still further evidence of the distinction between the present invention and the Olney disclosure is the fact that noribogaine is much less active than is ibogaine in binding to the NMDA receptor. See, the previously enclosed paper of Mash, et al., *Neurosciences Letters,* 192, 53-56 (1995). Thus, Olney teaches one of ordinary skill *away from* using ibogaine to treat nociceptive pain, i.e., pain which is treatable by an opioid agonist such as morphine (and now pursuant to the present invention, noribogaine) and further, that the person of ordinary skill would be taught away from using noribogaine to treat neuropathic pain as taught by Olney because of noribogaine's substantially reduced activity vis-à-vis the NMDA receptor, the target of the Olney disclosure. In sum, Olney clearly does not anticipate the present invention and the present methods are clearly distinguishable over the teachings of Olney.

As set forth in the declaration of Professor Mash, Olney at best teaches the use of ibogaine for treatment of NMDA mediated *neuropathic* pain. Within the context of the treatment of pain, one of ordinary skill would first look to an opioid agonist (morphine) to treat the pain and if the morphine was either ineffective or only *partially* effective in treating the pain, a neuropathic analgesic such as ibogaine also might be tried. See, for example the Hanks, reference, *ibid,* at page 719, lines 9-12 of the third full paragraph, which presupposes that opioid therapy will *invariably be part of the therapeutic regimen* in treating pain of mixed origin.

However, if the patient was suffering from nociceptive pain, then morphine would be used as the agent of choice, either alone or *possibly*, if a neuropathic component was also seen, in combination with ibogaine. However, even assuming the most favorable interpretation of the teachings of Olney, ibogaine would never be used or even *tried* for the treatment of nociceptive pain, given ibogaine's inactivity at the receptor (μ) which is required for such activity. Consequently, Olney cannot possibly be seen as anticipating the present invention.[2]

For the reasons presented above as supported by the Declaration of Dr. Deborah Mash, the present invention is clearly patentable over Olney.

The Rejection of Claims 6-9 As Being Obvious Over Olney, GB '897 in view of Hussain

Separately, the Examiner has rejected claims 6-9 under 35 U.S.C. §103 as being obvious over Olney and GB 841,697 ("GB '697"), in view of Hussain, U.S. No. 4,464,378 ("Hussain"). The Examiner argues that Olney teaches the use of ibogaine to treat pain and that GB '697 discloses that ibogaine is an analgesic agent useful in an analgesic composition for treating or alleviating pain. The Examiner relies on Hussain for teaching that opioid antagonists such as naloxone, naltrexone and nalorphine are well known analgesics and therefore useful in a method of treating or alleviating pain in a patient. The Examiner also acknowledges that noribogaine was known as a metabolite of ibogaine.

From a combination of the above three references, the Examiner concludes that it would have been obvious to one of ordinary skill in the art to employ noribogaine in combination with an opioid antagonist such as naloxone, nalterone and nalorphine in a method to alleviate pain and to optimize the effective amounts of active agents in the composition. Applicants respectfully traverse the Examiner's arguments.

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2 Note that the argument that in following the teachings of Olney, noribogaine as a metabolite of ibogaine would result in an inherent anticipation of the present invention also fails, inasmuch as there is no situation (other than an extremely unlikely inadvertent or accidental occurrence where nociceptive pain exists but is unrecognized because of apparent unresponsiveness to morphine) which could be contemplated where ibogaine would be used in the absence of morphine or other opioid agonist for the treatment of nociceptive pain, given ibogaine's art-recognized inactivity as an antinociceptive agent. Even if that were to occur, differences in pharmacokinetics/metabolism of ibogaine by the patient as a consequence of population genetics or other drugs or agents the patient was taking would not *necessarily and inevitably* result in quantities or concentrations of noribogaine which are effective to treat that incidental nociceptive pain. See the attached declaration of Dr. Deborah A. Mash.

As amended, claims 6-9 are directed to the use of a combination of noribogaine and an opioid antagonist in claimed amounts or delivered transdermally to treat or alleviate pain which is otherwise treatable by an opioid agonist (anti-nociceptive). A combination of Olney and GB '697 in view of Hussain, rather than rendering the present claims obvious, actually *teaches away* from the present invention.

Olney, discussed above, is directed to the use of ibogaine in the treatment of neuropathic pain by functioning as an antagonist of NMDA receptors. Olney specifically indicates in the abstract and specification, as discussed above, that ibogaine is used to treat pain which is *not* treatable with an opioid agonist such as morphine. As explained above, this is because Olney discovered that ibogaine acts as an antagonist of NMDA receptors. The present specification, in the examples at page 9-10, as well as the prior art cited, recognized that ibogaine has virtually no activity as an analgesic agent to treat pain in the same manner as morphine. There is simply no way to combine the references cited to render the present invention obvious.

None of the references teach that noribogaine has activity and is useful as an analgesic agent without the addiction exhibited by morphine to treat or alleviate nociceptive pain. Olney doesn't even mention noribogaine, and actually teaches away from using ibogaine to treat nociceptive pain which is mediated through μ receptors, through which opioid agonists and quite unexpectedly, noribogaine act to alleviate pain. GB '697 does not even recognize ibogaine as an analgesic agent and in particular confirms the teaching in Olney that ibogaine cannot be used to treat pain which is treatable using an opioid agonist.

GB '697 describes the use of a number of narcotic morphine analogs (including morphine) in combination with ibogaine or tabernanthine for analgesic use. GB '697 does not disclose noribogaine as an analgesic agent alone, and further only suggests the use of an addictive analgesic agent having morphine-like characteristics (i.e., an opioid analgesic) in combination with ibogaine or tabernanthine. However, as discussed herein, the combination of ibogaine with a morphine agonist (addictive analgesic) is not the present invention, which specifically uses noribogaine as a non-addictive analgesic (a receptor agonist) and avoids both ibogaine and addictive opioid receptor agonists such as morphine. In preferred embodiments of GB '697, as set forth in examples 1-2 5, 7-8 and 11, the use of morphine is described in

combination with ibogaine or tabernanthine. This teaching is in complete contrast to the present invention inasmuch as the present invention relies on noribogaine as a *nonaddictive* analgesic acting *alone* in the first instance, and when combined with another agent, that agent is an opioid *antagonist*- i.e., an *opioid inhibitor*, not an opioid *agonist* such as morphine. A review of the instant claims shows that Applicant specifically has disclaimed any subject matter which might read on the teachings of GB '697. Note that the present methods are used with noribogaine and an opioid antagonist, not ibogaine and an addictive opioid analgesic, such as morphine or a related opioid agonist. Thus, GB '697 clearly does not teach the present invention, for it fails to teach or suggest noribogaine even obliquely, and when it discloses ibogaine, ibogaine is disclosed *in combination* with another agent, that agent being the addictive analgesic agent morphine, which is an opioid agonist, not an opioid *antagonist* as claimed. Note that GB '695 clearly indicates at page 2, column 1, lines 5-6 that the art recognized that ibogaine per se did not have analgesic (anti-nociceptive) activity- i.e., *activity as a receptor agonist*, the receptors and action through which morphine acts to alleviate pain. GB '697 clearly does not obviate the deficiencies of Olney in failing to disclose or suggest the present invention. To the extent that Olney and GB '697 are combined, they provide no further enlightenment than GB '697 alone, i.e., that ibogaine may be used in combination with an *addictive* analgesic agent such as morphine, a combination which is clearly not the present invention.

Turning to Hussain, this reference completely fails to even disclose or suggest noribogaine and consequently, fails to disclose or suggest the present invention. In the present invention in claims 6-9, the use of noribogaine *in combination* with an opioid *antagonist* to treat pain is claimed. None of Olney, GB '697 or Hussain teaches that noribogaine may be used as an analgesic to treat nociceptive pain (which is mediated through a receptor) alone or in combination with an opioid antagonist. In fact, as set forth above, Olney teaches that ibogaine possesses no opioid analgesic activity, thus, the person of ordinary skill would not use ibogaine as an opioid analgesic. Hussain merely provides certain known compounds adapted for nasal administration, some of which are opioid agonists, some of which are opioid antagonists. Hussain does not obviate the deficiencies of Olney and GB '697. Moreover, the art does ***not*** recognize that opioid antagonists have analgesic activity, and it is respectfully submitted that opioid antagonists, such as naloxone and naltrexone, are not useful in the combination taught by GB '697, because they do not exhibit analgesic activity. That is

precisely why naloxone and naltrexone are referred to in the art as opioid *antagonists*. Opioid *agonists* such as morphine, not *antagonists*, such as naloxone and naltrexone, are the agents which exhibit analgesic activity and this is precisely why GB '697 teaches a combination of ibogaine and an opioid agonist analgesic, a combination which is not claimed by the present invention. Moreover, Hussain does not even mention noribogaine or ibogaine. Consequently, none of these references alone or in combination teaches or suggests the present invention and the present invention is non-obvious over the disclosure of these references.[3]

The present invention relates to the unexpected discovery that noribogaine, in contrast to ibogaine, may be used as an analgesic agent (i.e., noribogaine can be used to treat nociceptive pain which is treatable using an addictive opioid agonist such as morphine in a patient *without addiction*), either *alone* or in combination with an opioid *antagonist* as a particularly effective non-addictive analgesic. Thus, the present invention makes use of noribogaine's unique activity and represents a particularly effective method for alleviating pain, an advance in the art and an exciting improvement over the treatments of the prior art, given the lack of addiction associated with noribogaine's use. Methods which make use of noribogaine in combination with an opioid antagonist represent alternative embodiments of the present invention. Note that noribogaine is particularly effective as an analgesic agent because it is a full *mu* opioid agonist, is particularly effective in this regard, and is also *non-addictive*, in contrast to the opioid analgesics, i.e., the opioid agonists, such as morphine and related compounds. In addition, in contrast to ibogaine which evidences activity against neuropathic pain by inhibiting NMDA receptors, noribogaine exhibits vastly superior analgesic activity for pain as an *agonist* of the receptor similar to the effect of morphine (in fact, ibogaine is known in the art as possessing ***no*** significant analgesic activity on its own similar to noribogaine as taught by Olney and this is further born out by the examples on page 9-10 of

3 To the extent that the Examiner is somehow construing an obviouness argument based upon the view that naloxone and naltrexone, as taught by Hussain, can be combined with ibogaine as taught by GB '697 or Olney, to produce substantial non-addictive opioid analgesic activity because ibogaine, once in a patient's body will metabolize to noribogaine, that is simply not a cogent argument. As explained, the cited references actually ***teach away*** from such a combination. There is absolutely no suggestion in GB '697 that the use of ibogaine and an opioid antagonist would be an effective combination as an opioid analgesic and nothing in the art suggests that such a combination would be effective as an opioid analgesic given the clear teachings of Olney that ibogaine does not possess such activity and an opioid antagonist is generally known <u>not</u> to possess analgesic activity. Such a combination would be taught by the art not to work as an opioid analgesic. Notwithstanding that clear distinction, the co-administration of an opioid agonist with ibogaine also would substantially impair the ability of a patient to metabolize ibogaine to noribogaine in the first instance. See the enclosed Mash declaration at paragraph 32.

the instant specification). Moreover, noribogaine is free from the psychomimetic side effects of ibogaine, a deleterious side effect which limits ibogaine's use to treat unrelated (to the present invention) neuropathic pain. The present invention therefore represents a major advance in the treatment of nociceptive pain.

In contrast to the Examiner's arguments, the present invention is clearly patentable and non-obvious over the teachings relied upon by the Examiner. It is respectfully submitted by Applicant that Olney and GB '697 do not and cannot teach or suggest the present invention for the reasons presented above with reference to the attached declaration of Dr. Deborah Mash, and that Hussain, by failing to even mention the present invention, does not obviate the gross deficiencies of Olney and GB '697. The combination of references cited against the instant application fails to render the presently claimed invention unpatentable.

For the above reasons, Applicant respectfully asserts that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

Applicants have not added any claim and have cancelled 5 claims (one independent). Applicants previously have cancelled 15 claims (two independent) in the present application. No fee is therefore due for the presentation of this amendment. If any fee is due or any overpayment has been made, please charge/credit Deposit Account No. 04-0838. Should the Examiner wish to discuss the present application in an effort to advance its prosecution, the undersigned attorney may be reached at the telephone number set forth hereinbelow.

Respectfully submitted,
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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being sent by facsimile transmission to Examiner S.A. Jiang of group art unit 1617 at the United States Patent and Trademark Office on December 22, 2005.

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Henry D. Coleman